of claim 43, the method comprising:

a) exposing a sample comprising a polypeptide of claim 43 to a compound, and

b) detecting antagonist activity in the sample.

60. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a polynucleotide sequence of claim 52, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound. --

C1 Cont

REMARKS

New claims

By the above amendment, all pending claims have been canceled, without prejudice or disclaimer, and new claims 40-60 have been added. New claims 40-42, 46-50, 52-54, and 60 are drawn to the same polynucleotide invention as the previously allowed claims and should now be considered.

Failure to comply with 37 C.F.R. §§ 1.821 through 1.825 (Office Action page 3)

A corrected Sequence Listing is currently in preparation and will be submitted as soon as possible. This requirement is therefore requested to be held in abeyance.

Rejections under 35 U.S.C. § 101 and § 112, first paragraph (Office Action, pages 6-9)

A rejection has been set forth under 35 U.S.C. §101 and §112, first paragraph, based on allegations that "the claimed invention lacks patentable utility due to its not being supported by either [a] specific and/or substantial utility or a well established utility." The rejection is improper, as the claimed subject matter has a patentable utility as set forth in the instant specification, and a utility well-known to one of ordinary skill in the art.

I. Applicants' invention

The present invention includes, *inter alia*, polynucleotides encoding novel chemokines specifically expressed in the pancreas (PANEC-1 and PANEC-2, referred to collectively as PANEC).

PANEC shares a high degree of identity with known chemokines, including but limited to CC-chemokine and monocyte chemoattractant proteins 1, 2, and 3 (MCP-1, MCP-2, and MCP-3). BLAST2 reports based on recently available evidence clearly demonstrate that both PANEC-1 and PANEC-2 (SEQ ID NO:2, Library: 223187 and SEQ ID NO:4, Library:226152, respectively) share up to 100% identity with a number of human leukocyte-specific chemoattractant molecules (see enclosed BLAST2 reports with sequence alignments). In fact, *all* of the 30 top BLAST2 hits for each PANEC polypeptide (60 hits in total), are polypeptides that have been characterized as leukocyte-specific chemokines (see enclosed BLAST2 reports without alignments). Note that CC, MCP, SLP, TCA4, and EBI1, and eotaxin all refer to leukocyte specific chemokines. Applicants submit that one skilled in the art could not reasonably doubt that PANEC-1 and PANEC-2 are leukocyte-specific chemokines.

II. The use of PANEC or polynucleotides encoding PANEC to attract leukocytes *in vivo* to enhance local immune response is a specific utility under 35 U.S.C. § 101 and § 112, first paragraph

Applicants submit that the invention of the above identified application has specific utilities that have been overlooked or ignored by the Examiner. Based on the disclosure of the above identified application, a practitioner skilled in the art would know how to use the disclosed polynucleotide sequences (including but not limited to the polynucleotides of SEQ ID NO:1 and SEQ ID NO:3) to express leukocyte-specific chemokines (including but not limited to SEQ ID NO:2 and SEQ ID NO:4), isolate and purify the expressed polypeptides, and use the expressed polypeptides for attracting leukocytes to a region of the body in order to direct enhanced local immune response. One skilled in the art would also know how to deliver polynucleotides (including but not limited to SEQ ID NO:1 and SEQ ID NO:3) to target cells *in vivo*, using well known gene therapy delivery techniques (including but not limited to the use of adenovirus and retrovirus delivery vectors). Transduced cells would subsequently express a leukocyte-specific chemokine, resulting in the attraction of leukocytes to target cells and enhanced local immune response.

Under sections 101 and 112, first paragraph, of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v.*

> *Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

In the case of the instant application, the rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

III. Use of polynucleotides encoding PANEC for toxicology testing, drug discovery, and disease diagnosis are additional sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

In addition to the specific utilities described in § II, above, the mere fact that the PANEC-encoding polynucleotides of the instant application are expressed in human tissues (independent of their

specific functions as detailed above) immediately implies numerous practical and beneficial uses for the claimed invention in toxicology testing, drug development, and the diagnosis of disease. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary for the use of the polynucleotide in expression profiling. This fact notwithstanding, the knowledge that a polynucleotide encodes a leukocyte-specific chemokine, as is the case in the instant application, imparts an obvious importance to its expression pattern. For example, the fact that the expression profile of a chemokine is altered in a sample treated with a test compound is highly relevant in assessing the potential side effects of a drug intended to treat human disorders.

Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, *et al.*, Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra

Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir *et al.* describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. If the function of a polynucleotide is known, particularly if the function is as important as that of a chemokine, the value of the polynucleotide becomes even more obvious. Using the rapidly evolving gene expression array technologies available to a practitioner, the polynucleotide sequences disclosed in the instant application can readily be put to use, without undue experimentation, to obtain important expression profiling data.

There are numerous uses for the information made possible by expression profiling (some of which are mentioned above). Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling

leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

The rejections should be withdrawn at least because the Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease.

B. The use of PANEC for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is **not** conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra* (introduction to § II). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil* Co. v. *Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is **known** to be useful. It is not just a random sequence of speculative use. Because it is expressed in **humans**, a person of ordinary skill in the art would know how to use the claimed polynucleotide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the

polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of tumor suppressor proteins. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as leukemia or AIDS, affects the expression of leukocyte-specific chemokines and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polynucleotide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide or polynucleotide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

2. A patent applicant may specify a utility that applies to a broad class of inventions

Even if, *arguendo*, the claimed invention encoded a polypeptide that was a member of a broad class of human polypeptides (as the Office Action alleges on page 7, top), the polynucleotides of the instant application would possess substantial utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids

(concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a

practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (*i.e.,* which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, *e.g.,* for drug discovery purposes. This utility applies to all sequences actually expressed, yet in each case, the utility of the sequence is quite specific, *e.g.,* insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Leukocyte-specific chemokines, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, all of the leukocyte-specific chemokines expressed by humans can be used as tools for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of leukocyte-specific chemokines involved in the recruitment of leukocytes, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless expressed leukocyte-specific chemokines. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Because the use of PANEC in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. There is no authority for the proposition that use as a tool for research and disease diagnosis is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. Perhaps the value of certain polynucleotides in these databases is enhanced by their completeness and/or assigned function; however, each sequence in the database is independently valuable. The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other

sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

III. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶ ¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the case of the instant application, the claims are drawn, *inter alia*, to polynucleotides that

encode the leukocyte-specific chemokines PANEC-1 and PANEC-2 (SEQ ID NO:2 and SEQ ID NO:4, respectively). PANEC-1 and PANEC-2 are specifically expressed in the pancreas. The results of BLAST2 reports based on recently available evidence provide overwhelming support of Applicants' contention that PANEC-1 and PANEC-2 are leukocyte-specific cytokines (see enclosed BLAST2 reports). As leukocyte-specific cytokines, PANEC-1 and PANEC-2 have numerous "real world" utilities as described above.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Applicants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Applicants to rebut.

VI. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Junin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, even broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75). There is no evidence that cells express useless chemokines and no evidence to suggest that polynucleotides encoding PANEC would not be useful in attracting leukocytes to target cells, for toxicological screening, or for drug development.

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph,

is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be withdrawn.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Enablement rejection under 35 U.S.C. § 112, first paragraph (Office Action, pages 9-16)

Claims 38-39 (now canceled) were rejected under the first paragraph of 35 U.S.C. § 112 as allegedly being based on a disclosure which did not provide enablement commensurate in scope with the claims. The rejection is traversed to the extent that it may apply to the new method of detection claims 53 and 54.

The Office Action appeared to object to the "method of detection" claims primarily based on the definition of the nucleotide sequences recited by claims 36 and 37 (both now canceled). The target nucleotides recited by new claims 53 and 54 include polynucleotides of SEQ ID NO:1 and SEQ ID NO:3; naturally occurring polynucleotide sequences that hybridize under stringent conditions to the full length of SEQ ID NO:1 and SEQ ID NO:3; and complements of the foregoing. As recognized by the Examiner, "stringent hybridization conditions require a high percentage of complementarity in the range of 90-100% for stable hybridization." See the Office Action at page 16, last paragraph. Thus, the recitation of polynucleotide sequences which hybridize under stringent conditions to the full length of SEQ ID NO:1 or SEQ ID NO:3 addresses the scenario alluded to in the Office Action of the use of oligonucleotides which only possess limited sequence identity to SEQ ID NO:1 or SEQ ID NO:3.

Accordingly, withdrawal of this rejection is requested.

Written description rejection under 35 U.S.C. §112, first paragraph

The claims have been rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination

of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

a) Description of genomic sequences related to SEQ ID NO:1 and SEQ ID NO:3 is unnecessary

The Office Action has asserted, *inter alia*, that the present Specification provides an inadequate written description of the claimed subject matter because there is no description of a "full length gene sequence." By "full length gene sequence," the Action appears to be referring to a genomic sequence which encodes the polypeptide of SED ID NO:2 or SEQ ID NO:4 (although, note that in the present application "full length" is used to refer to a nucleic acid which contains a complete coding region for a polypeptide). However, those genomic sequences would likely include intron sequences as well as 5' and 3' regulatory and untranslated sequences. It is not necessary for the present Specification to describe such genomic sequences in order to satisfy the written description requirement of §112.

The present claims recite, for example, a polynucleotide comprising a naturally-occurring polynucleotide sequence which hybridizes under stringent conditions to the full length of SEQ ID NO:1 or SEQ ID NO:3, or complements thereof. SEQ ID NO:1 and SEQ ID NO:3 contain the coding regions for the polypeptides of SEQ ID NO:2 and SEQ ID NO:4, respectively. A description of 5' and 3' regulatory or untranslated regions of the genomic sequences is not essential to practice the claimed invention. It is well known to one of ordinary skill in the art that the coding region of a gene can be used to produce the encoded polypeptide, whether or not the native 5' and 3' regulatory regions and untranslated regions of that gene are present. For example, the coding sequence of SEQ ID NO:1 or SEQ ID NO:3 could be cloned into an expression vector under control of a heterologous promoter and the coding sequence expressed in an appropriate host organism. Consequently, a description of the genomic

sequences related to SEQ ID NO:1 and SEQ ID NO:3 is totally unnecessary.

b) The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1 and SEQ ID NO:3

The Office Action further notes that the claims encompass "sequences that hybridize to SEQ ID NOs: 1 or 3, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, and so forth" (Office Action at page 12). After an "analysis" of certain case law, the Action then concludes that the Specification fails to provide an adequate written description for the genus of polynucleotides claimed because "[t]he species specifically disclosed are not representative of the genus because the genus is highly variant" (Office Action at page 16). However, the subject matter encompassed by the claims is either disclosed by the Specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of new independent claim 40 recites "a polynucleotide sequence encoding a naturally-occurring amino acid sequence which hybridizes under stringent conditions to the full length of [a polynucleotide sequence encoding an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4]." Similar language appears in new independent claim 52.

The amino acid sequences of SEQ ID NO:2 and SEQ ID NO:4 are explicitly disclosed in the Specification. See, for example, Figures 1 and 2, respectively. One of skill in the art would know how to provide polynucleotide sequences encoding SEQ ID NO:2 and SEQ ID NO:4 as well as complements thereof. In this regard, the Specification also explicitly discloses the particular polynucleotide species of SEQ ID NO:1 and SEQ ID NO:3, which encode the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO:4, respectively (see Figures 1 and 2). Similarly, one of skill in the art would recognize polynucleotide sequences encoding variants of SEQ ID NO:2 and SEQ ID NO:4. The Specification further describes, *e.g.*, at page 9, last paragraph, naturally-occurring polynucleotide variants which hybridize under stringent conditions with nucleotide sequences which encode PANE-1 (*i.e.*, SEQ ID NO:2) and PANE-2 (*i.e.*, SEQ ID NO:4). Given SEQ ID NO:2 and SEQ ID NO:4, one skilled in the art would be able to describe polynucleotide sequences encoding variants of SEQ ID NO:2 and SEQ ID NO:4 which hybridize under stringent conditions to polynucleotides encoding SEQ ID NO:2 and SEQ ID NO:4. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

On pages 13-15 of the Office Action, there is a discussion of certain court decisions which attempts to justify the present rejection. This "analysis" is deficient in several ways. Perhaps most importantly, Office Action has failed to provide an appropriate written description inquiry based "***on***

whatever is now claimed," as directed in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

A. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin Cana" or "mammalian insulin Cana," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of functional features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant phasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

> In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:
>
> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular

DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. As discussed above, the "variant language" of independent claims 40 and 52 recites chemical structure to define the claimed genus:

> 40. An isolated polynucleotide comprising . . . b) a polynucleotide sequence encoding a naturally-occurring amino acid sequence which hybridizes under stringent conditions to the full length of [a polynucleotide sequence encoding ***an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4***] . . . (emphasis added)
>
> 52. An isolated polynucleotide comprising . . . b) a naturally-occurring polynucleotide sequence which hybridizes under stringent conditions to the full length of [***a polynucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3***] . . . (emphasis added)

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. There is no recitation of the functional characteristics of the claimed polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims to nucleic acids. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

B. The present claims do not define a genus which is "highly variant"

At page 16, the Office Action asserts that "[t]he species specifically disclosed are not representative of the genus because the genus is highly variant." The Action fails to provide any factual analysis to support this assertion and, on this basis alone, the rejection should be withdrawn. Consideration of available evidence illustrates that, rather than being highly variant, the claimed genus is

of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding chemokines related to the amino acid sequence of SEQ ID NO:2 and SEQ ID NO:4. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as chemokines and which have only 30% identity over at least 150 residues to SEQ ID NO:2 or SEQ ID NO:4. As recognized by the Examiner, "stringent hybridization conditions require a high percentage of complementarity in the range of 90-100% for stable hybridization." Office Action at page 16, last paragraph. The "variant language" of the present claims recites, for example, "a polynucleotide sequence encoding a naturally-occurring amino acid sequence which ***hybridizes under stringent conditions to the full length*** of [a polynucleotide sequence encoding an amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4]." Hence, the present claims encompass naturally-occurring polynucleotide variants which have at least about 90% sequence identity to polynucleotides encoding SEQ ID NO:2 or SEQ ID NO:4. This variation is far less than that of all potential chemokines related to SEQ ID NO:2 and SEQ ID NO:4, i.e., those chemokines having at least 30% identity over at least 150 residues to SEQ ID NO:2 or SEQ ID NO:4.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the DNA genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly* case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. There was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human

pre-proinsulin consisting essentially of a plus strand having the sequence:

5'-.sub.-24 GCL.sub.-23 X.sub.-22 TY.sub.-22 TGG.sub.-21 ATG.sub.-20 W.sub.-19
GZ.sub.-19 X.sub.-18 TY.sub.-18 X.sub.-17 TY.sub.-17 CCL.sub.-16
X.sub.-15TY.sub.-15 X.sub.-14 TY.sub.-14 GCL.sub.-13 X.sub.-12 TY.sub.-12
X.sub.-11 TY.sub.-11 GCL.sub.-10 X.sub.-9 TY.sub.-9 TGG.sub.-8 GGL.sub.-7
CCL.sub.-6GAK.sub.-5 CCL.sub.-4 GCL.sub.-3 GCL.sub.-2 GCL.sub.-1 TTK.sub.1
GTL.sub.2 AAK.sub.3 CAJ.sub.4 CAK.sub.5 X.sub.6 TY.sub.6 TGK.sub.7 GGL.sub.8
QR.sub.9 S.sub.9 CAK.sub.10 X.sub.11 TY.sub.11 GTL.sub.12 GAJ.sub.13 GCL.sub.14
X.sub.15 TY.sub.15 TAK.sub.16 X.sub.17 TY.sub.17 GTL.sub.18 TGK.sub.19
GCL.sub.20 GAJ.sub.21 W.sub.22 GZ.sub.22 GCL.sub.23 TTK.sub.24 TTK.sub.25
TAK.sub.26 ACL.sub.27 CCL.sub.28 AAJ.sub.29 ACL.sub.30 W.sub.31 GZ.sub.31
W.sub.32 GZ.sub.32 GAJ.sub.33 GCL.sub.34 GAJ.sub.35 GAK.sub.36 X.sub.37
TY.sub.37 CAJ.sub.38 GTL.sub.39 GGL.sub. 40 CAJ.sub.41 GTL.sub.42 GAJ.sub.43
X.sub.44 TY.sub.44 GGL.sub.45 GGL.sub.46 GGL.sub.47 CCL.sub.48 GGL.sub.49
GCL.sub.50 GGL.sub.51 QR.sub.52 S.sub.52 X.sub.53 TY.sub.53 CAJ.sub.54
CCL.sub.55 X.sub.56 TY.sub.56 GCL.sub.57 X.sub.58 TY.sub.58 GAJ.sub.59
GGL.sub.60 QR.sub.61 S.sub.61 X.sub.62 TY.sub.62 CAJ.sub.63 AAJ.sub.64 W.sub.65
GZ.sub.65 GGL.sub.66 ATM.sub.67 GTL.sub.68 GAJ.sub.69 CAJ.sub.70 TGK.sub.71
TGK.sub.72 ACL.sub.73 QR.sub.74 S.sub.74 ATM.sub.75 TGK.sub.76 QR.sub.77
S.sub.77 X.sub.78 TY.sub.78 TAK.sub.79 CAJ.sub.80 X.sub.81 TY.sub.81 GAJ.sub.82
AAK.sub.83 TAK.sub.84 TGK.sub.85 AAK.sub.86
TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAGAGAG
ATGGAATAAAGCCCTTGAACCA GC polyA-3'

wherein

A is deoxyadenyl,

G is deoxyguanyl,

C is deoxycytosyl,

T is thymidyl,

J is A or G;

K is T or C;

L is A, T, C, or G;

M is A, C or T;

X.sub.n is T or C if Y.sub.n is A or G; and C if Y.sub.n is C or T;

Y.sub.n is A, G, C or T if X.sub.n is C, and A or G if X.sub.n is T;

W.sub.n is C or A if Z.sub.n is G or A, and C if Z.sub.n is C or T;

Z.sub.n is A, G, C or T if W.sub.n is C, and A or G if W.sub.n is A;

QR.sub.n is TC if S.sub.n is A, G, C or T, and AG if S.sub.n is T or C;

S.sub.n is A, G, C or T if QR.sub.n is TC, and T or C if QR.sub.n is AG; and, subscript numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence with includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon $-GCL_{24}$ through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass naturally-occurring polynucleotide variants which have at least about 90% sequence identity to polynucleotides encoding SEQ ID NO:2 or SEQ ID NO:4. Clearly, then, the genus variation of the present claims is less than that of the claim of the '740 patent.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application February 17, 1995. Much has happened in the development of recombinant DNA technology in the 15 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this

application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 or SEQ ID NO:4. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids. In addition, the genus of DNA defined by the present claims is not "highly variant," as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the Specification provides an adequate written description of the claimed subject matter, and withdrawal of this rejection is therefore requested.

Rejection under 35 U.S.C. § 102(b) (Office Action, pages 16-17)

Claims 36 and 37 (now canceled) were rejected under 35 U.S.C. § 102(b) as being anticipated by Esposito *et al.* [(1988) J. Biol. Chem. 263:11466-11472]. Independent claim 40 now recites, *inter alia*, "a polynucleotide sequence encoding a naturally-occurring polynucleotide sequence which hybridizes under stringent conditions to the full length" of a polynucleotide of SEQ ID NO:1 or SEQ ID NO:3, and polynucleotide complements thereof. Comparable language is found in independent claim 52. Esposito *et al.* does not describe a nucleic acid pertinent to these claims.

As recognized by the Examiner, "stringent hybridization conditions require a high percentage of complementarity in the range of 90-100% for stable hybridization." See the Office Action at page 16, last paragraph. The new claims recite, *inter alia*, a polynucleotide sequence which hybridizes under stringent conditions to the full length of a polynucleotide sequence encoding SEQ ID NO:2 or SEQ ID NO:4 and complements thereof. Esposito *et al.* does not describe a polynucleotide capable of such "full length hydridization" under stringent conditions, i.e., a polynucleotide having 90% or greater sequence identity over the full length of a polynucleotide sequence encoding SEQ ID NO:2 or SEQ ID NO:4.

Therefore, withdrawal of the 35 U.S.C. §102(b) rejection is requested.

CONCLUSION

For at least the above reasons, it is submitted that the present application is fully in condition for allowance and withdrawal of the outstanding rejections is requested. Early notice to that effect is earnestly solicited. If the Examiner contemplates other actions, or if a telephone conversation would expedite allowance of the claims, the Examiner is invited to contact the undersigned.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108. This form is enclosed in duplicate.**

Respectfully submitted,
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